

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|--|---|
| Date of mailing (day/month/year) 09 February 2000 (09.02.00) | |
| International application No. PCT/US99/10040 | Applicant's or agent's file reference P3986 089044 |
| International filing date (day/month/year) 07 May 1999 (07.05.99) | Priority date (day/month/year) 12 June 1998 (12.06.98) |
| Applicant GOKE, Burkhard et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

05 January 2000 (05.01.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Olivia RANAIVOJAONA Telephone No.: (41-22) 338.83.38 |
|---|---|

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

SEASE, Edmund, J.
 Zarley, McKee, Thomte, Voorhees &
 Sease
 Suite 3200
 801 Grand Avenue
 Des Moines, IA 50309-2721
 ÉTATS-UNIS D'AMÉRIQUE

| |
|---------------------------------------|
| Date of mailing (day/month/year) |
| 03 December 1999 (03.12.99) |
| Applicant's or agent's file reference |
| P3986 089044 |
| International application No. |
| PCT/US99/10040 |

IMPORTANT NOTIFICATION

International filing date (day/month/year)
 07 May 1999 (07.05.99)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

| | | |
|------------------|----------------------|--------------------|
| Name and Address | State of Nationality | State of Residence |
| | | |
| | Telephone No. | |
| | | |
| | Facsimile No. | |
| | | |
| | Teleprinter No. | |
| | | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

| | | |
|--|----------------------|--------------------|
| Name and Address | State of Nationality | State of Residence |
| COOLIDGE, Thomas, R. 3820 N.W. 46th Street Lincoln, NE 68524 <i>NE</i> United States of America | US | US |
| | Telephone No. | |
| | | |
| | Facsimile No. | |
| | | |
| | Teleprinter No. | |
| | | |

3. Further observations, if necessary:

Additional inventor and applicant for US only has been recorded.

4. A copy of this notification has been sent to:

| | |
|--|--|
| <input checked="" type="checkbox"/> the receiving Office | <input checked="" type="checkbox"/> the designated Offices concerned |
| <input type="checkbox"/> the International Searching Authority | <input type="checkbox"/> the elected Offices concerned |
| <input type="checkbox"/> the International Preliminary Examining Authority | <input type="checkbox"/> other: |

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer H. Zhou Telephone No.: (41-22) 338.83.38 |
|---|---|

PATENT COOPERATION TREATY

PCT

6P
INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|--|--|
| Applicant's or agent's file reference P3986 089044 | FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small> | |
| International application No. PCT/US 99/ 10040 | International filing date (day/month/year) 07/05/1999 | (Earliest) Priority Date (day/month/year) 12/06/1998 |
| Applicant BIONEBRASKA, INC. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **4** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

GLUCAGON-LIKE PEPTIDE-1 IMPROVES BETA-CELL RESPONSE TO GLUCOSE IN SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 10040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10040

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | RACHMAN J ET AL: "Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM." DIABETOLOGIA, (1997 FEB) 40 (2) 205-11. , XP002122529 the whole document ---- | 1-38 |
| X | CAVAGHAN M K ET AL: "Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 530-7. , XP002122530 the whole document ---- | 1-38 -/- |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 November 1999

Date of mailing of the international search report

26/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Moreau, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | WO 98 08531 A (ELI LILLY AND COMPANY) 5 March 1998 (1998-03-05) page 23 -page 24 ----- | 1,39,40 |
| P, X | BYRNE M M ET AL: "Glucagon - like peptide 1 improves the ability of the beta - cell to sense and respond to glucose in subjects with impaired glucose tolerance." DIABETES, (1998 AUG) 47 (8) 1259-65. , XP002122531 the whole document ----- | 1-40 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10040

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|--|--|
| WO 9808531 A | 05-03-1998 | AU 4163897 A NO 990916 A PL 331986 A ZA 9707756 A | 19-03-1998 29-04-1999 16-08-1999 10-09-1998 |

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|--|---|
| Applicant's or agent's file reference P3986 089044 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US99/10040 | International filing date (day/month/year) 07/05/1999 | Priority date (day/month/year) 12/06/1998 |
| International Patent Classification (IPC) or national classification and IPC A61K38/26 | | |
| Applicant BIONEBRASKA, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|--|---|
| Date of submission of the demand 05/01/2000 | Date of completion of this report 12.07.2000 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Ludwig, G Telephone No. +49 89 2399 8698 |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10040

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-24 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.
 claims Nos. 10-40.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/10040

the said international application, or the said claims Nos. 10-40 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|--|
| Novelty (N) | Yes: Claims 1-40 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims |
| | No: Claims 1-40 |
| Industrial applicability (IA) | Yes: Claims 1-9 (10-40 - cf. separate sheet) |
| | No: Claims |

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/10040

Reference is made to the following documents:

D1: **P-document** - BYRNE M M ET AL: 'Glucagon - like peptide 1 improves the ability of the beta - cell to sense and respond to glucose in subjects with impaired glucose tolerance.' DIABETES, (1998 AUG) 47 (8) 1259-65. , XP002122531

D2: RACHMAN J ET AL: 'Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM.' DIABETOLOGIA, (1997 FEB) 40 (2) 205-11. , XP002122529

D3: WO 98/08531

Item V:

1. If the priority of the application is *not* valid P-document D1 which discloses the essence of the application would be used against novelty/inventive step of the application.
2. Document D2 discloses the use of glucagon-like peptide-1 (GLP-1) for the treatment of NIDDM.

Insofar as patients afflicted with non-insulin dependent diabetes (NIDDM) also have an **impaired glucose tolerance (IGT)** claims 10-38 (method of treatment of IGT by a compound which binds to a receptor for GLP-1, i.e. as for instance GLP-1) are not regarded as inventive in view of document D2.

However, a disclaimer excluding treatment of NIDDM would appear to establish an inventive step in these claims.

3. Pharmaceutical compositions comprising GLP-1 (= a compound binding to the receptor for GLP-1) are known from document D2. Document D3 discloses pharmaceutical compositions comprising GLP-1 or analogs/derivatives.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/10040

There appears to be no evidence for a substantial difference between the composition of claim 1 and those disclosed by document D2 or D3, respectively.

Nothing inventive can therefore be seen in claims 1-9 directed to (pharmaceutical) compositions vis-a-vis these documents.

4. For the assessment of the present claims 10-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item III:

5. Claims 10-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10040

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | RACHMAN J ET AL: "Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM." DIABETOLOGIA, (1997 FEB) 40 (2) 205-11. , XP002122529 the whole document --- | 1-38 |
| X | CAVAGHAN M K ET AL: "Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 530-7. , XP002122530 the whole document --- -/- | 1-38 |

 Further documents are listed in the continuation of box C Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 November 1999

Date of mailing of the international search report

26/11/1999

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Moreau, J

INTL INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|----------|---|----------------------|
| X | WO 98 08531 A (ELI LILLY AND COMPANY) 5 March 1998 (1998-03-05) page 23 -page 24 | 1,39,40 |
| P,X | BYRNE M M ET AL: "Glucagon - like peptide 1 improves the ability of the beta - cell to sense and respond to glucose in subjects with impaired glucose tolerance." DIABETES, (1998 AUG) 47 (8) 1259-65. , XP002122531 the whole document | 1-40 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 10040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10040

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|------------|------------------------|
| WO 9808531 | A 05-03-1998 | AU 4163897 A | 19-03-1998 | NO 990916 A 29-04-1999 |